



Cirrhosis

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Objectives

- Diagnosis of cirrhosis
- Etiologies of cirrhosis
- Compensated versus decompensated disease
- Evidence-based monitoring for patients with cirrhosis
- Management of complications

Case

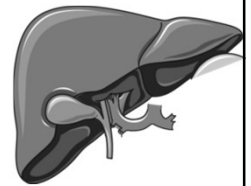
A 61-year-old man comes to see you in your primary care clinic to establish care. He has a history of hypertension and hyperlipidemia. You obtain routine labs and notice that his *AST and ALT are mildly elevated*. You obtain a RUQ ultrasound which notes *hepatic steatosis* and a *nodular liver contour*.

Have you confirmed a diagnosis of cirrhosis?



The Normal Liver

- Hepatocytes arranged in a hexagonal arrangement surrounding a central vein.
 - Lobules
- Dual blood supply
 - Portal vein (75%)
 - Hepatic artery (25%)
- Largest internal organ in the body!



PMID: 29112863

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Functions of the Liver

- Bilirubin metabolism
 - Bilirubin conjugation and secretion as bile
- Protein metabolism
 - Synthesis of proteins (albumin)
 - Breaks down protein via urea cycle
- Synthesis of coagulation factors
- Fat soluble vitamin storage
- Glycogenesis and gluconeogenesis

What Is Cirrhosis?

- Hepatic fibrosis at its latest stage
- Progressive fibrosis which has led to nodule formation and distorted hepatic architecture
- Sometimes referred to as "F4 fibrosis"
- Liver often retains full function

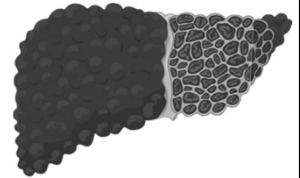


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What Is Cirrhosis...For Patients



How To Diagnose Cirrhosis

- Based on a combination of factors
- Labs can *suggest* cirrhosis, but no single lab makes the diagnosis
 - Patients with compensated cirrhosis usually have normal labs
- Imaging showing a nodular liver contour can be diagnostic
 - May also see: caudate lobe hypertrophy, portal hypertension

A Review of Imaging Modalities

- Ultrasound: inexpensive and widely available
 - May miss “early” cirrhosis
- CT and MRI: need contrast for optimal evaluation
 - Not routinely used for diagnosis



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A Review of Imaging Modalities

- Transient elastography (FibroScan): no morphologic assessment
 - Limitations with truncal obesity, active alcohol use, active viral hepatitis, congestion from cardiac disease
- MRI elastography: most accurate in terms of noninvasive fibrosis tests



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The Role of Liver Biopsy

- Remains gold standard for the diagnosis of cirrhosis
- Can be performed in multiple ways
 - Subcutaneous
 - Transjugular – can also measure pressures
 - Endoscopic ultrasound
- Sampling error still occurs!
- Generally avoided unless discordant imaging or need to confirm etiology

Case

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Have you confirmed a diagnosis of cirrhosis?

YES

Case: Continued

You let the patient know about his cirrhosis diagnosis. He is shocked and has several questions for you. What could have caused this? He is not a drinker. How can he have cirrhosis when he has had yearly checkups and has never been informed of liver issues?

How can you best answer him?



The Big 3 (in the US)

MASH

Alcohol

HCV

MASLD/MASH

- Fastest growing cause of chronic liver disease worldwide
- Defined as hepatic steatosis (on imaging or biopsy) PLUS a cardiometabolic risk factor
 - HTN
 - BMI >25 (or >23 in Asian patients)
 - Type II diabetes
 - HLD
- Many patients will not have elevated liver enzymes (especially if cirrhotic)

PMD: 36727674

What happened to NASH?

- In 2023, worldwide liver societies announced new nomenclature for steatotic liver disease
- NAFLD -> MASLD (metabolic-dysfunction-associated steatotic liver disease)
- NASH -> MASH (metabolic dysfunction-associated steatohepatitis)
- Goal to remove the term “nonalcoholic” and its associated stigma

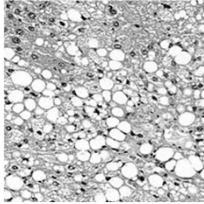


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Alcohol-Associated Liver Disease

- Significant alcohol consumption leading to liver disease
- Steatosis -> steatohepatitis -> cirrhosis
- Diagnosis primarily based on history though should suspect if:
 - AST: ALT >2:1
 - Hepatic steatosis (without metabolic risk factors)



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Clinical Pearl: PEth

- Phosphatidylethanol (PEth) is a serum biomarker used to detect alcohol use
- Measures phospholipid produced when ethanol is metabolized
- Reliably detects alcohol use over the past 4 weeks
 - High sensitivity and specificity
- *Important to discuss measurement with your patients*

PMID: 37569551

Hepatitis C

- Only about 20% of patients will naturally clear HCV infection
- Cirrhosis takes decades to develop though may progress more quickly in some patients
 - Older patients
 - MASLD overlap
- All patients >18 should be screened for HCV and referred for treatment if positive



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Hepatitis B

- Leading cause worldwide of cirrhosis
 - Endemic in Southeast Asia and Sub-Saharan Africa
- Patients at high risk for cirrhosis progression:
 - High viral load
 - Alcohol use
 - Older age at infection
 - Coinfection with HCV, HDV, HIV
- Treatment well-tolerated

PMID: 41186418

Autoimmune Liver Disease

- Autoimmune Hepatitis
 - Primarily young and middle-aged women
 - With treatment, risk for development to cirrhosis is low
- Primary Sclerosing Cholangitis
 - Progressive cholestatic disease most common in men
 - Associated with IBD (usually ulcerative colitis)
- Primary Biliary Cholangitis
 - Female-predominant cholestatic liver disease

Clinical Pearl: ASMA

- **Anti-smooth muscle antibody** is a useful tool but often causes confusion
- Classically associated with autoimmune hepatitis
- Poor specificity overall especially at low titers (1:40 or lower)
- Positive in up to 30% of patients with MASLD
- Remember that AIH can only be diagnosed with liver biopsy

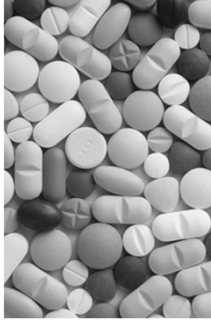


Genetic Causes

- Alpha 1 antitrypsin deficiency
 - Heterozygosity can increase risk of progression to cirrhosis from other causes
- Hemochromatosis
 - Suspect if TSAT >50% and elevated ferritin
- Wilson disease
 - Young patient with psychiatric symptoms
 - Caution that ceruloplasmin may be low due to copper deficiency

Other Considerations

- Cardiac cirrhosis
 - Consider in patients with right-sided heart failure or severe HFrEF
- Medication injury
 - Amiodarone, methotrexate
- Infiltrative diseases
 - Sarcoidosis or amyloidosis
- Budd-Chiari syndrome



The Serologic Workup

- In all patients with a new diagnosis of cirrhosis, send a serologic workup
- Chronic hepatitis panel, ANA, anti-smooth muscle Ab, quantitative Ig (IgG, IgA, IgM), A1AT level and phenotype, iron panel, anti-mitochondrial antibody, ceruloplasmin (if <55), PETH (if available)
- **The presence of an obvious diagnosis does not preclude a second diagnosis**

Cryptogenic Cirrhosis

- Cirrhosis without discernable cause
- Often "burnt out MASH"
 - Steatosis no longer present on imaging or even biopsy
- Biopsy can be considered but would ask if management would change



Case: Continued

Your serologic workup is unrevealing, and you conclude that the etiology of your patient's cirrhosis is MASH.

He would like to know "how bad" his cirrhosis is and what he can expect moving forward.

What do you say?



Compensated Cirrhosis

- Compensated cirrhosis is the presence of cirrhosis WITHOUT impaired liver function
- Patients are often diagnosed in this stage and are usually asymptomatic
- Reasonable prognosis especially if underlying cause is treated
 - Alcohol avoidance
 - Viral hepatitis treatment
 - Weight loss

PMD: 37771878

CSPH: the “in between”

- Some patients develop clinically significant portal hypertension in the absence of decompensation
- Suggested by
 - Varices on endoscopy
 - Splenomegaly
 - Thrombocytopenia
 - Liver stiffness > 25 on elastography
 - HVPG >10
- Patients with CSPH are at higher risk of decompensation

Decompensated Cirrhosis

- Either complications of portal hypertension or synthetic dysfunction of the liver
- Patients with cirrhosis PLUS
 - Ascites
 - Variceal bleeding (varices alone ≠ decompensation)
 - Hepatic encephalopathy
 - Jaundice

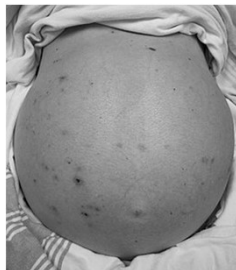
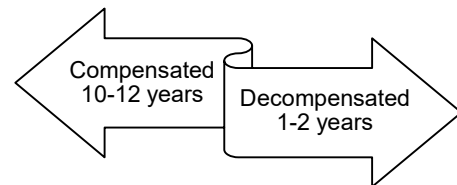


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What is the Prognosis?

- Wide gap prognostically between compensated and decompensated disease
- Median survival:



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Can Cirrhosis Be Reversed?

- The simple answer: we don't know
- Patients with compensated cirrhosis may see some regression in fibrosis
 - Likely will still have risk of complications
- Patients with decompensated cirrhosis can "recompensate"
 - Typically seen in treatment of underlying cause
 - Most common in ALD with sobriety

Case: Continued

You discuss with the patient that he appears to have compensated cirrhosis. You recommend weight loss and lifestyle changes and discuss his prognosis with him.

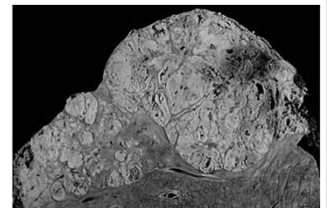
Since his disease is currently compensated, you decide to manage him in your primary care clinic.

What should you order?

Management of Cirrhosis

Hepatocellular Carcinoma

- Patients with cirrhosis have a ~2% annual risk of developing HCC
- **All patients** with cirrhosis require HCC screening
- Per AASLD guidelines:
 - Imaging (RUQ US) and AFP every 6 months



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Hepatocellular Carcinoma

- Estimated that only ~25% of patients receive appropriate screening
 - Early-stage HCC has a 50-70% 5-year survival
 - Very early-stage disease with curative options
- Vast options for HCC treatment if identified early
 - Resection, radiation, ablation, immunotherapy, and liver transplantation
- Essential to speak to patients about this risk

PMID: 37199193

Variceal Screening

- Generally, all patients with cirrhosis should undergo screening for esophageal varices
- Performed via upper endoscopy
- Large varices should be managed by either band ligation OR with nonselective beta blocker
- Small varices warrant repeat surveillance yearly



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Baveno Guidelines

Baveno VII – Renewing consensus in portal hypertension

Roberto de Franchis^{1*}, Jaime Bosch^{2,3}, Guadalupe Garcia-Tsao^{4,5}, Thomas Reiberger^{6,7}, Cristina Ripoll⁸, on behalf of the Baveno VII Faculty⁹

- Can forego EGD in cirrhotic patients with
 - Platelet count >150,000
 - Liver stiffness <20 kPa
- Goal is to reduce unnecessary procedures in low-risk patients

PMID: 35120736

Case: Continued

Your patient undergoes an EGD at your recommendation.

This shows small esophageal varices. You discuss with him that this confirms CSPH.

He is concerned about this and wonders if there are any options to prevent progression to decompensated disease.

What could you recommend?

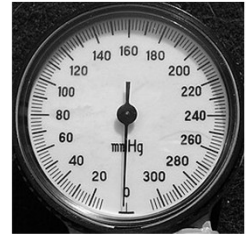
Nonselective Beta Blockers

- Nadolol, propranolol, and carvedilol
 - Nadolol and propranolol must be titrated to HR <60
 - Increased preference for carvedilol
 - Goal dose is 6.25 mg BID
- Indications include
 - Primary variceal prophylaxis
 - Secondary prophylaxis following variceal hemorrhage
 - **Patients with CSPH (to avoid decompensation)**

PMID: 35120736

Nonselective Beta Blockers

- Stop in patients with SBP <90 OR with side effects
- Would avoid in patients with:
 - Refractory ascites
 - Significant renal dysfunction (related to liver disease)



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Variceal Hemorrhage

- Most commonly due to esophageal varices but can also be due to gastric varices
- Requires urgent hospital evaluation and EGD within 12 hours
- Long term management
 - Serial EGD with band ligation
 - NSBB

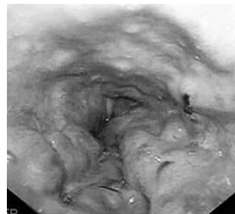


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Ascites

- Accumulation of fluid in the peritoneal cavity due to portal hypertension
- First episode warrants diagnostic (+/-) therapeutic paracentesis
 - Confirms cirrhosis, rule out infection
 - SAAG >1.1 consistent with portal hypertension
- Management
 - 2 g sodium restriction
 - Diuretics

Refractory Ascites

- May be due to
 - Electrolyte derangements
 - Renal injury
 - Resistance to diuretics
- Consider TIPS in patients with low MELD (<20), no hepatic encephalopathy
- Increased mortality in patients >70

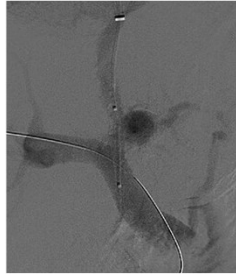


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Hepatic Encephalopathy

- Complication related to hepatic dysfunction (inability to metabolize ammonia) and portal hypertension (shunting)
- May be subtle at first
 - Poor sleep
 - Mild forgetfulness
- Treat with lactulose
 - Titrated to 3-4 BMs per day
- Rifaximin can be added if lactulose ineffective alone

Hepatic Encephalopathy

- Common HE triggers
 - GI bleeding
 - Electrolyte abnormalities or AKI
 - Infection
- Lactulose adherence is challenging. Consider Miralax as an alternative

Comparative Effectiveness and Safety of Polyethylene Glycol Electrolyte Solution Versus Lactulose for Treatment of Hepatic Encephalopathy
A Systematic Review and Meta-analysis

Clinical Pearl: Ammonia

- Venous ammonia has limited clinical value in the diagnosis or treatment of HE
- Levels do not correlate with symptoms
 - Normal does not rule out HE
- Levels may fluctuate
 - Renal function
 - Muscle mass

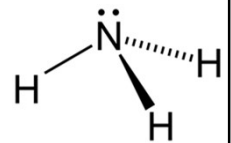


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Sarcopenia

- Related to increased metabolic demand, reduced PO intake, and malabsorption
- Significant complication of decompensated cirrhosis
 - Present in majority of patients
 - Increased mortality
- Recommend high protein intake ~1.5 g/kg/day
- Resistance training (+/- PT)



Normal Sarcopenia
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PMID: 32934043

Liver Transplantation

- Any decompensating event -> referral to hepatology (ideally a transplant center)
- Consider OLT in any patient with decompensated cirrhosis and MELD >15
- HCC also an indication for OLT in select patients



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Liver Transplantation

- Evaluation for OLT
 - Cardiac and pulmonary evaluation
 - Psychosocial evaluation
 - Age-appropriate cancer screening
- Common contraindications
 - Age above 75 with relative contraindications above 70
 - Active substance use
 - Active extrahepatic malignancy

Take Home Points

- The diagnosis of cirrhosis can be made with imaging alone
- MASLD, alcohol-associated liver disease, and HCV are the leading causes of cirrhosis in the United States
- Cirrhosis and liver failure are not synonymous
- **All patients** with cirrhosis require HCC screening
- Decompensated cirrhosis warrants referral to hepatology